UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,263	01/05/2000	KEVIN A. JARRELL	0342941-0043	1459

7590 05/23/2005

BRENDA HERSCHBACH JARRELL
CHOATE HALL & STEWART
EXCHANGE PLACE
53 STATE STREET
BOSTON, MA 02109-2891

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/478,263	JARRELL ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed January 10, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-3 and 5-21 were pending. Applicants amended claims 1, 7, 14 and 15. In addition, Applicants added claims 22-23. Therefore, claims 1-3 and 5-23 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. The rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

5. Claims 1-3 and 5-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978)). Applicants' claims are directed to a broad genus of methods for the combinatorial biosynthesis of unspecified compounds. Here, Applicants provide no structural limitations for the "starter units", "handles" and "solid supports" used in conjunction with the method. In addition, Applicants biosynthetic enzymatic machinery includes an unknown number of enzymes and/or enzymatic machinery system constituents drawn to the modified polyketide synthetases, natural and modified peptide synthetases, natural and modified terpene synthases and natural and modified animal fatty acid synthases (e.g., see newly amended claim 1). Furthermore, no limitations are provided for the "synthetic organic chemistry" that is further used to diversify the biosynthetic products (e.g., see claim 1, step d). Thus, Applicants are claiming virtually an infinite number of methods for producing virtually an infinite number of compounds.

In contrast, Applicants' specification does not even provide a single working example (i.e., no *quid pro quo* here). Although, Applicants' specification provides a limited number starter units, handles and solid supports that could "potentially" be used in the claimed method (e.g., see figures), the

evidence suggests that these experiments were never performed. In support of this position the Examiner notes that no biological activities and/or physical characterization is presented in the specification for any compounds that might otherwise indicate the success and/or failure of the claimed method.

Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding adequate disclosure. For adequate disclosure, like enablement, requires ***representative examples***, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. In addition, when there is ***substantial variation within the genus***, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05).

Here, the variation within the genus would be enormous because no limitations have been placed on the starter units, handles and/or solid phase resins. Furthermore, no limitations have been placed on the type of synthetic organic chemistry that would subsequently be employed to further modify the compounds. In addition, a review of the literature indicates that combinatorial

biosynthesis is a new and highly unpredictable field that requires identification/characterization of the "modular biosynthetic enzymatic machinery." With the exception of polyketides and nonribosomally produced peptides and carbohydrates, this has not been done. For example, Taylor states that for the biosynthesis of epothione would require a mixed NRPS/PKS "biosynthetic enzymatic machinery." However, Taylor states that there are currently "no examples of such an approach [in the literature]" and that while it may be "easy to imagine how novel epothione analogs could be generated", "[m]uch work remains to be done in elucidating the organization and structure of hybrid PKSs/NRPSs, however, before combinatorial biosynthesis with these systems can be undertaken" (emphasis added) (see Taylor, S. V. in "Handbook of Combinatorial Chemistry" Eds. Nicolaou, K. C.; Hanko, R.; Hartwig, W. Weinheim Germany: Wiley-VCH 2002, Vol. 2, page 1075, last paragraph). In addition, Darby states that enzymatic synthesis in general is severely limited by that enzymes narrow substrate specificity and, as a result, it is unclear whether Applicants claimed starter units, functional handles, etc. would even act as substrates for the vast majority of enzymes in those enzymatic pathways (e.g., see Dalby, page 1, lines 15-20, "However, the use of enzymes in the synthesis of complex molecules is currently hindered by the time taken to discover or develop an enzyme with the required substrate specificity ... identifying a suitable biocatalyst is ***extremely difficult***, as the known enzymes often do not show activity towards the desired substrate"; see also lines 27-28, "it is much more difficult to find an ... enzyme with activity towards a particular substrate, due to

the high substrate specificity exhibited by most natural enzymes"; see also page 17, paragraph 1 wherein the narrow substrate specificity for transketolase is set forth that would presumably fall within the scope of Applicants' claims because it is useful in producing polyketides). Therefore, even a greater showing would be required to reflect the variation within the genus in accordance with MPEP § 2163.05, which has not been done.

Furthermore, it should be noted that Applicants never claim a "screening" step that would otherwise allow a person of skill in the art to sort through and find a "useful" compound and/or library from the large number of compounds that would unquestionably result from the claimed method (i.e., no "screening step" is provided in any of the current claims). In *University of Rochester v. G.D. Searle & Co., Inc.* (U.S. Court of Appeals Federal Circuit (CAFC) 358 F.3d 916, 69 USPQ2d 1886 (Fed.Cir.2004)), a method for selectively inhibiting PGHS-2 enzymatic activity failed to meet the written description requirement because the patent "neither disclose[d] any such compound nor provide[d] any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research." *Id.* at 2 (quoting *University of Rochester versus G.D. Searle and Co., Inc.*, 249 F.Supp.2d at 220). Here, Applicants have similarly failed to disclose any "useful" compounds and/or libraries (e.g., no biological activities have been set forth in the specification). Consequently, any method for producing such a library would likewise be defective because that library would still need to be screened by "trial-and-error" methods to determine whether it was useful. Thus, Applicants have not disclosed any methods for producing a library of

compounds that would not require "trial-and-error" screening in violation of *Rochester*.

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention. Applicants do not even provide a single working example of this method (i.e., no compounds have been produced and/or tested). The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variable, Applicants prophetic teachings are insufficient to describe this enormous genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. *See Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir. 1993); *See also Brenner v. Manso*n, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting, "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Here, Applicants appear to be merely setting forth a research plan (i.e., use some unspecified compound with a laundry list of potential enzymatic pathways to produce products that have not yet been isolated and/or characterized and then perform some further unspecified synthetic organic chemistry on said uncharacterized/isolated compounds in hopes that it will produce a useful result).

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that is often not desirable to possess common structural features between library members (e.g., see 9/16/04 Response, paragraph bridging pages 19-20).

[2] Applicants argue that their newly amended claims are now more narrowly drawn such that a person of skill in the art would know what "starter units" would be required by the Markush of enzymatic machinery that was added to the claim (e.g., see 9/16/04 Response, page 11, paragraph 2). Applicants also argue that they have "incorporated by reference" several publications disclosing "known" modified enzymatic machinery (e.g., see 9/16/04, page 11, paragraph 3). In support of this position Applicants note that they "have disclosed that polyketide synthases [that] will accept starter units that have a thioester group and that these starter units can be used to generate template structures such as those shown in Figure 1 ... that a terpene synthase will utilize starter units that are derivatives of farnesyl pyrophosphate ... when the enzymatic machinery is a peptide synthetase, the starter unit should be an amino acid derivative" (e.g., see 9/16/04 Response pages 11-12).

[3] Applicants argue that they have "indicated that functional starter units that will be accepted by the selected enzymatic machinery can be identified by presenting a

random set of starter units having a common structural feature to an enzymatic machinery system" (e.g., see 9/16/04 Response, page 12, paragraph 3).

[4] Applicants argue that they "... have disclosed that the template molecules produced by the enzymatic machinery are selected or designed to have latent functionalities that can be functionalized using synthetic organic chemistry" and provide several examples of such functionalization (e.g., see 9/16/04 Response, paragraph bridging pages 12-13).

[5] Applicants argue, "Applicants use the antibody recognition element to purify the products of the enzymatic machinery. Therefore, Applicants' invention is not limited to any particular antibody recognition element" (e.g., see 9/16/04 Response, page 13, first full paragraph).

[6] Applicants argue that they have "listed in the specification the properties which a solid support should have to be useful" (e.g., see 9/16/04 Response, page 13 second full paragraph).

[7] Applicants argue that they have "... described how to select starter units that are compatible with a particular enzymatic machinery" (e.g., 9/16/04 Response, paragraph bridging pages 13-14).

[8] Applicants argue with regard to the new claims that they have "... disclosed common structural features for starter units that are accepted by polyketide synthase and peptide synthetase had have described in the specification the specific reactions used to modify the template structures ... [thus] Applicants had possession" (e.g., see pages 14-15, section 2).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully contends that Applicants' have misinterpreted the Examiner's argument. Generation of diversity is not at issue. The issue is whether enough "common features" are known that would allow a person of skill in the art to extend the limited teachings of their specification to other more unpredictable art areas that are currently being claimed. As noted above (e.g., see the Taylor reference), combinatorial biosynthetic chemistry is unpredictable art especially when the enzymatic machinery has not yet been characterized. Consequently even if, *assuming arguendo*, Applicants had set forth some concrete data indicating that they had made some useful compounds by this method (which is not the case), a person of skill in the art would not be able to extend those teachings to other areas because the art is diverse and unpredictable.

[2] The Examiner agrees that Applicants' more narrowly drawn claims would allow a person of skill in the art to predict with greater clarity the types of starting materials that could "possibly" interact with the art recognized "known" enzymatic machineries. However, this would not allow a person to predict *a priori* if the potential substrate would lead to a useful "product" as is required by the claims (i.e., none of the claims disclose a "screening" step that would otherwise allow a person of skill in the art to narrow down the huge number of compounds that would be produced by the method to a "useful" result). Furthermore, a person of skill in the art would not be able to predict whether a particular enzyme would react with a known substrate when the "handle" is attached. Thus, even if a person of skill in the art were only to use "known" substrate/enzyme pairs, he or she would not be able to predict whether that known substrate would be able to interact with that same enzyme when a "handle" was attached

i.e., the handle may simply prevent binding of any compound to the known enzyme (e.g., see Dalby, page 1, lines 15-20, "However, the use of enzymes in the synthesis of complex molecules is currently hindered by the time taken to discover or develop an enzyme with the required substrate specificity ... identifying a suitable biocatalyst is ***extremely difficult***, as the known enzymes often do not show activity towards the desired substrate"; see also lines 27-28, "it is much more difficult to find an ... enzyme with activity towards a particular substrate, sue to the high substrate specificity exhibited by most natural enzymes [e.g., natural and modified polyketide synthases, natural and modified peptide synthases, etc.]"; see also page 17, paragraph 1 wherein the narrow substrate specificity for transketolase is set forth that would presumably fall within the scope of Applicants' claims because it is useful in producing polketides). Furthermore, none of the publications that have been "incorporated by reference" use Applicants' claimed starter unit-handle compounds and thus a person of skill in the art would not know whether those compounds would act as substrate in accordance with the teachings of Dalby set forth above.

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "presenting a random set of starter units having a common structural feature to an enzymatic machinery system" i.e., a "screening" step) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicants' arguments are not commensurate in scope with the claims.

[4] The Examiner contends that a person of skill in the art would not know how to narrow the laundry list of potential synthetic organic chemistry reactions to generate a "useful" library. Applicants are not claiming a "screening" method (i.e., there is no screening step in any of the claims). Thus, Applicants must disclose method steps that will lead to the production of a "useful" library. However, Applicants have not disclosed such a library nor have they disclosed with any specificity a sequence of organic synthetic transformations that would lead to such a library. In addition, it is unclear whether Applicants' modified templates would even act as substrates for the vast majority of enzymes making up the laundry list of claimed biosynthetic machinery (e.g., see arguments with respect to the Darby reference above).

[6] The Examiner contends that Applicants have listed properties that might be useful in a "screening" method, but have failed to list properties that will lead to the production of a useful library without first performing such a screening method. In addition, it is unclear whether Applicants' solid supports and/or the handles would even act as substrates for the vast majority of enzymes making up the laundry list of claimed biosynthetic machinery (e.g., see arguments with respect to the Darby reference above).

[7] The Examiner respectfully disagrees. The Darby reference (see amended rejection above) clearly shows that most natural enzymes have a very narrow substrate specificity and, as a result, it is not at all clear whether Applicants modified starter units would even act as substrates. Furthermore, the Taylor reference indicates that combinatorial biosynthesis is even more unpredictable especially when dealing with modified enzymes. Finally, even if assuming arguendo that Applicants did provide starter units that were compatible with the specified enzymatic machinery, this showing

would be of no consequence because Applicants have not provided any showing that those compatible substrates would lead to useful products in violation of the *Rochester* decision i.e., Applicants' are not claiming a "screening" method, but method for "producing" compounds (e.g., see newly amended rejection above).

[9] The Examiner contends that all of the arguments that were previously applied to the original claims are equally applicable to the newly added claims (see sections **[1]** through **[8]** above). For example, none of Applicants' claims recite a "screening" step and, as a result, a person of skill in the art would not be able to select a "useful" compound and/or library from the large number of compounds that would be produced from the claimed method. In addition, Applicants have not provided any evidence that said polyketide synthase and/or peptide synthetase enzymatic systems would even interact with the modified starter units and a person of skill in the art would not reasonably believe that such an interaction would occur because enzymes have very narrow substrate specificity, as exemplified by Darby.

Accordingly, the written description rejection cited above is hereby maintained.

7. Claims 1-3 and 5-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for ***any*** of Applicants' currently claimed embodiments. Applicants have not provided ***any*** examples and, as a result, a person of skill in the art would not know how to practice the claimed invention to produce a "useful" result without undue experimentation. This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention:

Applicants' claims are directed to a broad genus of methods for the combinatorial biosynthesis of unspecified compounds. Here, Applicants provide no structural limitations for the "starter units", "handles" and "solid supports" used in conjunction with the method. In addition, Applicants biosynthetic enzymatic machinery includes an unknown number of enzymes and/or enzymatic machinery system constituents drawn to the modified polyketide synthetases, natural and modified peptide synthetases, natural and modified terpene synthases and natural and modified animal fatty acid synthases (e.g., see newly amended claim 1). Furthermore, no limitations are provided for the "synthetic organic chemistry" that is further used to diversify the biosynthetic products (e.g., see claim 1, step d). Thus, Applicants are claiming virtually an infinite number of methods for producing virtually an infinite number of compounds. Consequently, the nature

of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: While combinatorial biosynthesis has been known for some time, there are no examples of "solid phase" combinatorial biosynthesis. Therefore, the Examiner contends that the level of predictability in the art is low or absent.

A person of skill in the art would not know how to pick "solid supports" and/or "handles" that would insure a reaction between a "biosynthetic enzymatic machinery system" and modified "starter units" (e.g., see Dalby, page 1, lines 15-20, "However, the use of enzymes in the synthesis of complex molecules is currently hindered by the time taken to discover or develop an enzyme with the required substrate specificity ... identifying a suitable biocatalyst is ***extremely difficult***, as the known enzymes often do not show activity towards the desired substrate"; see also lines 27-28, "it is much more difficult to find an ... enzyme with activity towards a particular substrate, due to the high substrate specificity exhibited by most natural enzymes"; see also page 17, paragraph 1 wherein the narrow substrate specificity for transketolase is set forth that would presumably fall within the scope of Applicants' claims because it is useful in producing polketides). Furthermore, while the art shows that in some cases the "biosynthetic enzymatic machinery" has relaxed specificity and thus could accommodate a wider array of substrates, it does not show that the enzymes could accommodate substrates on a solid support like a bead or a chip. How would a "support bound

starter unit" get transferred from one enzyme to the next in the modular biosynthetic enzymatic machinery when it is bound to a reaction bead?

Furthermore, combinatorial biosynthesis is a new and highly unpredictable field that requires identification/characterization of the "modular biosynthetic enzymatic machinery." With the exception of polyketides and nonribosomally produced peptides and carbohydrates, this has not been done. For example, Taylor states that for the biosynthesis of epothione would require a mixed NRPS/PKS "biosynthetic enzymatic machinery." However, Taylor states that there are currently "no examples of such an approach [in the literature]" and that while it may be "easy to imagine how novel epothione analogs could be generated", "[m]uch work remains to be done in elucidating the organization and structure of hybrid PKSs/NRPSs, however, before combinatorial biosynthesis with these systems can be undertaken" (emphasis added) (see Taylor, S. V. in "Handbook of Combinatorial Chemistry" Eds. Nicolaou, K. C.; Hanko, R.; Hartwig, W. Weinheim Germany: Wiley-VCH 2002, Vol. 2, page 1075, last paragraph). Therefore, Applicants are clearly not enabled for systems like PKS/NRPS wherein the "biosynthetic enzymatic machinery" has not yet been characterized.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided a single working example of this method with any specificity. For example, the specification does not disclose

reagents and products that are essential for the method including examples of a "support bound starter unit", "template structure", "species of template structure after functionalization", "nonnatural natural product", "antibody recognition element" (e.g., see Applicants' response, Paper No. 19, page 2, "Applicants have not specified any species of solid support unit through out the specification and the claims"; see also page 3, paragraph 1, "Applicants have not indicated in the specification or claims any species of template"; see also page 3, paragraph 4, "Applicants have not indicated in the specification or claims any particular species of template after functionalization"; see also page 4, last paragraph, "Applicants have not indicated in the specification or claims any particular species of nonnatural natural product") (emphasis added).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant

disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response

8. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that their newly amended claims are now more narrowly drawn such that a person of skill in the art would know what "starter units" would be required by the Markush of enzymatic machinery that was added to the claim (e.g., see 9/16/04 Response, page 11, paragraph 2). Applicants also argue that they have "incorporated by reference" several publications disclosing "known" modified enzymatic machinery (e.g., see 9/16/04, page 11, paragraph 3). In support of this position Applicants note that they "have disclosed that polyketide synthases [that] will accept starter units that have a thioester group and that these starter units can be used to generate template structures such as those shown in Figure 1 ... that a terpene synthase will utilize starter units that are derivatives of farnesyl pyrophosphate ... when the enzymatic machinery is a peptide synthetase, the starter unit should be an amino acid derivative" (e.g., see 9/16/04 Response pages 15-16).

[2] Applicants argue that they have "indicated that functional starter units that will be accepted by the selected enzymatic machinery can be identified by presenting a random set of starter units having a common structural feature to an enzymatic machinery system" (e.g., see 9/16/04 Response, paragraph bridging pages 16-17).

[3] Applicants argue that they "... have disclosed synthetic organic chemistry reactions that can be used to functionalize particular latent functionalities of a template molecule" and provide several "potential" examples of such functionalization (e.g., see 9/16/04 Response, page 17, middle paragraph).

[4] Applicants argue, "Applicants use the antibody recognition element to purify the products of the enzymatic machinery. Therefore, Applicants' invention is not limited to any particular antibody recognition element" (e.g., see 9/16/04 Response, page 13, first full paragraph).

[5] Applicants argue that they have "... amended the claims to indicate that the starter units are provided to the enzymatic machinery *in vitro*" (e.g., see 9/16/04 Response, page 18, paragraph 1).

[6] Applicants argue, "In the instant case, evidence indicates that biosynthetic enzymatic machinery systems can tolerate a broad variation in starter units which supports Applicants' disclosure ... the Examiner has not provided any evidence to the contrary" (e.g., see 9/16/04 response, page 18).

[7] Applicants argue that they have "disclosed in the specification the properties which a solid support should have to be useful" (e.g., see 9/16/04 Response, paragraph bridging pages 18-19).

[8] Applicants argue that they have "... described how to select starter units that are compatible with a particular enzymatic machinery" (e.g., 9/16/04 Response, page 19, first full paragraph).

[9] Applicants argue with regard to the new claims that they have "... teaches the type of starter units to be used with peptide synthetase ... and polyketide synthase ... [etc.]" (e.g., see page 19, section 3).

This is not found persuasive for the following reasons:

[1] The Examiner agrees that Applicants' more narrowly drawn claims would allow a person of skill in the art to predict with greater clarity the types of starting materials that could "possibly" interact with the art recognized "known" enzymatic machineries. However, this would not allow a person to predict *a priori* if the potential substrate would lead to a useful "product" as is required by the claims (i.e., none of the claims disclose a "screening" step that would otherwise allow a person of skill in the art to narrow down the huge number of compounds that would be produced by the method to a "useful" result). Furthermore, a person of skill in the art would not be able to predict whether a particular enzyme would react with a known substrate when the "handle" is attached. Thus, even if a person of skill in the art were only to use "known" substrate/enzyme pairs, he or she would not be able to predict whether that known substrate would be able to interact with that same enzyme when a "handle" was attached i.e., the handle may simply prevent binding of any compound to the known enzyme (e.g., see Dalby, page 1, lines 15-20, "However, the use of enzymes in the synthesis of complex molecules is currently hindered by the time taken to discover or develop an enzyme with the required substrate specificity ... identifying a suitable biocatalyst is

extremely difficult, as the known enzymes often do not show activity towards the desired substrate"; see also lines 27-28, "it is much more difficult to find an ... enzyme with activity towards a particular substrate, sue to the high substrate specificity exhibited by most natural enzymes [e.g., natural and modified polyketide synthases, natural and modified peptide synthases, etc.]"; see also page 17, paragraph 1 wherein the narrow substrate specificity for transketolase is set forth that would presumably fall within the scope of Applicants' claims because it is useful in producing polketides). To this end the Examiner notes that none of the publications that have been "incorporated by reference" use Applicants' claimed starter unit-handle compounds and thus a person of skill in the art would not know whether those compounds would act as substrate in accordance with the teachings of Dalby.

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "presenting a random set of starter units having a common structural feature to an enzymatic machinery system" i.e., a "screening" step) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicants' arguments are not commensurate in scope with the claims.

[3] The Examiner contends that a person of skill in the art would not know how to narrow the laundry list of potential synthetic organic chemistry reactions to generate a "useful" library. Applicants are not claiming a "screening" method (i.e., there is no screening step in any of the claims). Thus, Applicants must disclose method steps that

will lead to the production of a "useful" library. However, Applicants have not disclosed such a library nor have they disclosed with any specificity a sequence of organic synthetic transformations that would lead to such a library. In addition, it is unclear whether Applicants' modified templates would even act as substrates for the vast majority of enzymes making up the laundry list of claimed biosynthetic machinery (e.g., see arguments with respect to the Darby reference above).

[4] The Examiner reiterates that Applicants are not claiming a "screening" method and, as a result, Applicants' arguments are moot. Applicants have only disclosed what might work (i.e., properties that might be useful for antibody recognition and/or solid supports) if it were to be screened successfully, not what actually has worked.

[5] The Examiner agrees that Applicants' amendment satisfactorily obviates this portion of the rejection and, as a result, the rejection has been amended accordingly.

[6] The Examiner sets forth the Dalby reference as requested (see newly amended rejection above) for the sole purpose of rebutting Applicants' arguments that the biosynthetic enzymes would tolerate a "broad variation" of starter units. Thus, the Examiner's burden of proof has been met. In addition, the Examiner notes that the Weissman et al. reference (exhibit C) only refers to a specific class of enzymes and thus is not commensurate in scope with the claims. In addition, the article notes that many changes even for this narrow class of enzymes "completely abolished" activity (e.g., see Weissman et al. results). Furthermore, the article indicates that "many factors" are involved in predicting substrate specificity thus further complicating the analysis (e.g., see Weissman et al., column 2, last paragraph; see also page 748, column 1, paragraph 1, wherein the authors seem to suggest that the PKS represent merely an anomaly to the

general rule that enzymes have narrow substrate specificity, "The data presented here demonstrate that under the chosen conditions in vitro, the same range of starter unit structure can be incorporated through either unnatural starter acids or their corresponding diketides, even though the erythromycin loading domain has been thought to have a restricted specificity [i.e., the enzymes used in Weissman represent the "exception" not the "rule"]"; see also reference 33 in Weissman which calls this broad specificity "remarkable"). Thus, the Weissman et al. reference only serves to reinforce the teachings of Dalby, which indicate that most enzymes do not have a wide substrate specificity and it is "extremely difficult" to identify such enzymes for a given substrate (see newly amended rejection above).

[7] The Examiner contends that Applicants have listed properties that might be useful in a "screening" method, but have failed to list properties that will lead to the production of a useful library without first performing such a screening method. In addition, it is unclear whether Applicants' solid supports and/or the handles would even act as substrates for the vast majority of enzymes making up the laundry list of claimed biosynthetic machinery (e.g., see arguments with respect to the Darby reference above).

[8] The Examiner respectfully disagrees. The Darby reference (see amended rejection above) clearly shows that most natural enzymes have a very narrow substrate specificity and, as a result, it is not at all clear whether Applicants modified starter units would even act as substrates. Furthermore, the Taylor reference indicates that combinatorial biosynthesis is even more unpredictable especially when dealing with modified enzymes. Finally, even if assuming arguendo that Applicants did provide starter units that were compatible with the specified enzymatic machinery, this showing

would be of no consequence because Applicants have not provided any showing that those compatible substrates would lead to useful products in violation of the *Rochester* decision i.e., Applicants' are not claiming a "screening" method, but method for "producing" compounds (e.g., see newly amended rejection above).

[9] The Examiner contends that all of the arguments that were previously applied to the original claims are equally applicable to the newly added claims (see sections **[1]** through **[8]** above). For example, none of Applicants' claims recite a "screening" step and, as a result, a person of skill in the art would not be able to select a "useful" compound and/or library from the large number of compounds that would be produced from the claimed method. In addition, Applicants have not provided any evidence that said polyketide synthase and/or peptide synthesis enzymatic systems would even interact with the modified starter units and a person of skill in the art would not reasonably believe that such an interaction would occur because enzymes have very narrow substrate specificity, as exemplified by Darby.

Accordingly, the Enablement rejection cited above is hereby maintained.

New Rejections

9. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. In newly amended claim 7, to the extent that removal of the phrase "chemically robust" extends beyond the "robust" handles (i.e., reads on non-robust and robust), the increased breadth of possible modification constitutes new matter, since there is no specification support or original claim support for such scope; nor has applicant provided any indication where such support exists.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 14, 2005

BENNETT CELSA
PRIMARY EXAMINER